Shear wave elastography of breast cancer

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Shear Wave Elastography of breast cancer: sensitivity according to histological type in a large cohort

KEY WORDS

Breast cancer

Ultrasound

Shear wave elastography

Histological type

Size

Abstract

Purpose: to define the shear wave elastography (SWE) characteristics of breast cancer histological types by size in a large cohort.

Methods: consecutive patients with US visible masses underwent SWE. All those with confirmed invasive breast cancer were included in the study. Histologic type was ascertained from core biopsy and surgical resection specimens. For each type, mean and median values for Emean and Emax were ascertained. Commoner tumor types were further analysed by invasive size. The significance of differences was established using the Chi-square test.

Results: 1137 tumors constituted the study group. The proportion of tumors with Emean below 50kPa was higher in tubular cancers (23%) compared to ductal carcinomas of no specific type (DNST) (6%) ($p<0.001$). Emax below 80kPa was seen in in 34% of tubular cancers compared to 16% of DNST ($p<0.002$). Emean and Emax for lobular, mucinous, papillary and metaplastic cancers were not different from those of DNST. There were no significant differences in Emean or Emax between tumor types once broken down according to invasive size.

Conclusions: Most breast cancer histological types have similar SWE characteristics. The exception is tubular cancer which has significantly lower stiffness than other histologic types, accounted for largely by their small size.

Key points

1. Tubular cancers are softer than other tumours types.
2. Lobular cancers have shearwave features similar to those of ductal carcinomas.
3. Differences in shearwave findings of different tumour types are related to size.

Introduction

Shearwave elastography (SWE) has been shown to be a useful adjunct to grayscale ultrasound in benign/malignant differentiation of solid masses identified on grayscale ultrasound (1, 2). Stiffness on SWE has been shown to be related to histologic size, grade, nodal stage and immunohistochemical characteristics (3-5). Imaging modalities often have different sensitivities for different tumor histological types within the same organ due to differences in morphology, growth pattern and neovascularisation. Mammography, ultrasound and MRI have been shown to have reduced sensitivity for the detection and sizing of lobular breast cancers compared to ductal carcinomas of no specific type (6-8). Mucinous cancers have also been shown to be over-represented in false negative interval cancers following screening mammography (9, 10).

Previous studies have suggested that lobular cancers have similar SWE characteristics to ductal carcinomas of no specific type (DNST) and that tubular cancers are more frequently soft on SWE compared to other cancers (11-13). However, these studies have been too small to give definitive answers regarding these tumor types and very little has been published regarding the SWE features of rarer types such as papillary, mucinous and metaplastic carcinomas. The aim of this study is to define the SWE characteristics of tumor histologic types in a large cohort of breast cancers and to analyse SWE sensitivity by both tumor type and size for the commoner histologic variants.

Methods

SWE has been part of the routine breast ultrasound examination of solid breast masses at our institution since November 2009. Quantitative data is routinely recorded prospectively at the time of the examination. In accordance with the applicable National Research Ethics Service guidance, ethical approval for this retrospective study of prospectively acquired anonymised data was not required (National Research Ethics Service, 2008) (14). However, written informed consent to use images was obtained, according to routine practice.

All consecutive patients with US visible masses were scanned using the Aixplorer ultrasound system (SuperSonic Imagine^{TM}, Aix en Provence, France) between 29 December 2010 and 04 April 2015. Those patients with discrete masses on grayscale US, subjected to needle core biopsy and/or surgical biopsy which confirmed invasive breast cancer were included in this study.

All patients were scanned and biopsied with ultrasound guidance by one of five breast radiologists or an advanced radiography practitioner trained to perform and interpret breast ultrasound. These practitioners had between 7 and 22 years of breast ultrasound experience and had at least 3 months experience of performing SWE of solid breast lesions. Greyscale and elastography images were obtained during the standard ultrasound appointment. Four SWE images in two orthogonal planes were obtained. The ROI utilized in all cases was 2mm in diameter. For benign/malignant differentiation, threshold values of 50 kilopascals (kPa) and 80kPa were used for mean elasticity (Emean) and maximum elasticity (Emax) respectively, as these values have been validated in previous studies (1, 15). The average of the 4 values from the 4 images was used for analysis. SD values were also recorded.

Histologic type was ascertained initially from core biopsy samples and then confirmed at surgical resection. In 170 women confirmation at surgery could not be done for a number of reasons including women with severe comorbidities who did not undergo surgical resection, women still undergoing neo-adjuvant therapy and women with a pathologic complete response following neoadjuvant chemotherapy. Type was assigned according to

national pathology reporting guidelines (16). Histologic invasive size was recorded in those women who underwent immediate surgical excision.

The mean and median values for Emean and Emax and the percentage of cancers with stiffness below the cut-off values were ascertained for each tumor type. Types with more than 20 tumors assigned were further analysed according to invasive size in patients treated by immediate surgery. The significance of differences was established using the Chi-square test.

Results

1137 tumors in 1112 women constituted the study group. The mean age was 62.9 years (range 24.5-95.3 yrs.). 37% of the tumors were screen detected while 63% were symptomatic. Twelve lesions did not have the Emax results recorded, leaving 1125 lesions with Emax results for analysis.

Emean results

The Emean characteristics of the study group according to histologic type are shown in Table 1. The proportion of tumors with Emean values below the cut off of 50kPa was significantly higher in tubular cancers (23%) compared to DNSTs (6%), $p<0.001$. Lobular, mucinous, papillary and metaplastic cancers had Emean values which were not significantly different from DNSTs. None of the rarer subtypes had tumors with benign Emean characteristics, but the numbers of each type are too small to draw firm conclusions. Table 2 shows the Emean values of the commoner tumor types, treated by immediate surgery, broken down by type and invasive size. Smaller tumors of all types except mucinous cancers had similar rates of false negative Emean findings. All mucinous cancers of whatever size had Emean values above 50 kPa. There were no statistically significant differences in Emean between tumor types once broken down according to invasive size.

Emax results

The Emax characteristics of the study group according to histologic type are shown in Table 3. The proportion of tumors with Emax below the cut off of 80kPa was significantly higher in tubular cancers (34%) compared to DNSTs (16%) $p<0.002$. Lobular, mucinous, papillary and metaplastic cancers had Emax characteristics which were not significantly different from DNSTs. Although some of the rarer subtypes had tumors with benign Emax values, the numbers of each type are too small to draw firm conclusions. Table 4 shows the Emax characteristics of the commoner tumor types, treated by immediate surgery, broken down

by type and invasive size. Smaller tumors of all types had similar rates of false negative Emax findings. There were no statistically significant differences in Emax between tumor types once broken down according to invasive size.

No significant differences were found between the SD values of lobular and ductal carcinomas of no specific type.

Discussion

We have found that most breast cancer histologic types have similar SWE characteristics. In particular, lobular cancers have similar stiffness patterns to DNSTs. The exception is tubular cancer which more frequently demonstrates stiffness in the benign range for Emean and Emax than other histologic types. There is also a non-significant trend for mucinous cancers to be stiffer than all other tumour types.

The low stiffness of tubular cancers is mostly explained by their small size at diagnosis compared to other histologic types. Tables 2 and 4 demonstrate that proportion of soft tubular cancers 10mm or less in size is not significantly different than that of other histologic types of this size. Tubular cancers are however much more frequently small compared to other histologic types (17), leading to an overall decrease in the sensitivity of SWE for the detection of tubular cancers compared to other histological types. A number of previous studies have shown that low grade cancers are less stiff than high grade cancers even when size is taken into account (2,5). This also may contribute to the low stiffness of tubular cancers, which are always grade 1 compared to other tumor types. As tubular cancers are usually found at screening mammography rather than presenting symptomatically, the negative predictive value of SWE in screening practice is, not surprisingly, less than in symptomatic practice (11).

Lobular cancers are difficult to detect and size accurately on mammography, grayscale US and even on MRI (6-8). This is thought in part to be because of the diffuse growth pattern of lobular cancers which is due to loss of E-cadherin, a cell adhesion molecule and in part to the infrequent presence of calcifications (18). We have found that lobular cancers are as

well detected on SWE as DNSTs and that this is true even when the size of the cancers is taken into account. Previous studies have also shown that lobular cancers have similar SWE characteristics to ductal cancer (2, 11, 19). Indeed, a recent study has shown a significant increase in sensitivity for the diagnosis of symptomatic lobular cancers if SWE is added to mammography and grayscale US (13). It has been suggested that differences in heterogeneity may exist between lobular cancers and ductal carcinomas of no specific type. However we found no significant difference in SD values (a measure of heterogeneity) between these two tumour types. The ROI used in this study (2mm) was small and it is possible that a larger ROI size may pick up heterogeniety differences not detectable with a small ROI.

The finding that mucinous cancers are at least as stiff as other tumor types is surprising. Mucinous cancers are thought to be soft due to presence of mucin with the cancer. However, the highest stiffness associated with cancers is usually at the tumor/stromal interface or in the peritumoral stroma, and high stiffness in tumor-associated stroma may well be the explanation of the stiffness of mucinous cancers. Other groups have also found high stiffness associated with the small numbers of mucinous cancers they have studied (2, 19).

Th vast majority of invasive papillary cancers are stiff despite papillary cancers being predominantly low grade and the frequent presence of a cystic component. What is as yet unknown is whether SWE is useful in differentiating intracystic/in situ papillary cancers from invasive cancers, as only invasive cancer have been included in this study.

The strengths of this study are in the large number of cancers (approximately 3 times the size of the previous largest study) and the prospective data collection. One weakness is that it is a from a single center with a research interest in SWE, so it is possible that our results may not be generalizable to routine practice. However, SWE is not a difficult technique and good reproducibility has been reported previously (20,21). SWE can only be performed if a lesion is seen first on grayscale US or if a focal palpable abnormality is present. This means that SWE studies have, by definition, excluded cancers which are neither palpable nor visible on greyscale US.

The results of the study confirm the findings of previous studies that small cancers are often soft and fail to reach threshold values of Emean and Emax used for benign/malignant differentiation. It has been noted previously that small benign lesions are also soft compared to large benign lesions (22). This suggests that altering thresholds of stiffness used for benign/malignant differentiation according to the size of the lesion might lead to improved performance of SWE when characterising small lesions. Previous studies have also noted that the qualitative pattern of stiffness seen in benign and malignant lesions are different (23, 24). It is possible that characterization using such patterns of stiffness could improve the clinical utility of SWE in the differentiation of small benign and malignant masses.

In conclusion, tubular cancers are significantly more likely than other tumor types to show benign SWE features but this is largely due to the small size of tubular cancers at presentation.

Declarations of Interest

AE has a PhD student partly funded by Supersonic Imagine and has delivered presentations for Supersonic Imagine.

The other authors declare no conflict of interest

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